Clotting Pharmacology

Introduction

This lesson is about the pharmacology of clotting. More precisely, the pharmacology of opposing clotting. In Clotting #2: *Thrombophilia* we introduced the idea of the arterial platelet clot and the venous factor thrombus. We will carry that concept into the medications used to treat those conditions. The pharmacology of clotting is divided into antiplatelets (which treat arterial platelet clots) and anticoagulants (which treat venous factor thrombi). Antiplatelets target primary hemostasis; anticoagulants target secondary hemostasis. And then, at the end, we throw in the wild card, fibrinolytics.

Primary hemostasis is all about the **platelet plug**. Arterial platelet clots occur secondary to high-stress forces superimposed on diseased blood vessels. This high-flow, high-pressure system results in clots rich predominantly in **platelets**. The main disease that causes acceleration of primary hemostasis or that results from an arterial thrombus, is atherosclerosis. We prevent atherosclerotic plaque rupture with **antiplatelets**. Antiplatelets can cause **platelet bleeding**—superficial bleeding, microhemorrhages resulting in petechiae, gingival bleeding, and menorrhagia. That means we want you lumping the following together: primary hemostasis, arterial platelet clot, atherosclerotic vascular disease, platelets, antiplatelets, platelet bleeding.

Secondary hemostasis is all about the **fibrin thrombus.** Venous clots occur secondary to impaired flow through the veins. This is a low-flow, low-pressure system where blood accumulates, pooling, resulting in thrombi rich in **fibrin**. The main disease that results from acceleration of secondary hemostasis is deep vein thrombosis (DVT), and therefore also pulmonary embolism (PE). We treat DVT/PE with **anticoagulation**. Anticoagulants can cause **factor bleeding—**deep bleeding, macrohemorrhages, resulting in hemarthrosis and hematomas. That means we want you lumping the following together: secondary hemostasis, venous factor thrombosis, DVT/PE, anticoagulants, factors, factor bleeding.

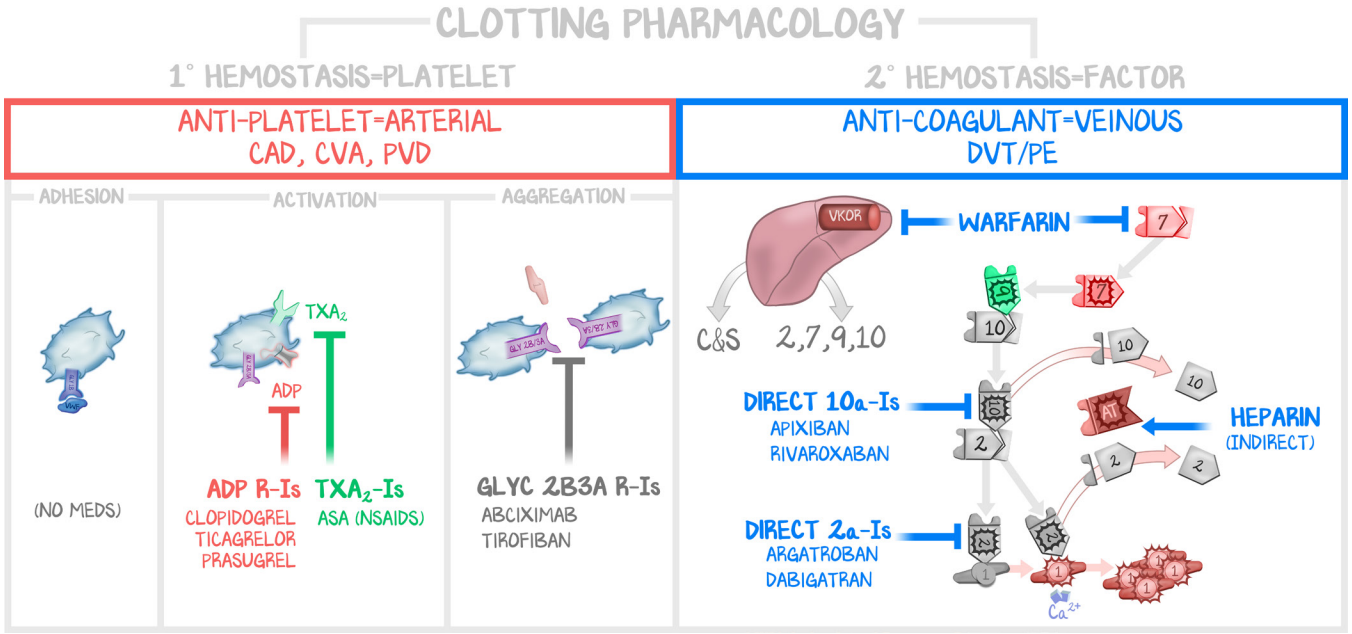

Figure 3.1: Organizing Clotting Pharmacology
While exceptions exist, keeping these medications, pathways, and disease states polarized promotes understanding and retention. Strokes are caused by arterial clots, but receive tPA (the clot buster) to alleviate the acute symptoms. Strokes are treated chronically with antiplatelets. Heart attacks are caused by arterial clots, and do receive aspirin at presentation, but also heparin, which we teach you is an anticoagulant. Finally, when it comes to clots of the ventricles (mural thrombi, AFib stroke prophylaxis, prosthetic valves), we use anticoagulants, even though the ventricles are high-pressure systems.

Anticoagulants #1: Heparins

Heparins are considered **indirect thrombin inhibitors** because the target of the molecule is not thrombin, but rather **antithrombin**. Heparin binds to and induces a conformational change in antithrombin, which increases the affinity of the active protease site a hundredfold for activated thrombin and activated factor 10. Antithrombin inhibits factor 10 and factor 2 (thrombin). Heparin helps antithrombin do that better. In making the conformational change, heparin is not consumed, and is released from one antithrombin to bind another antithrombin.

Heparin comes in three forms: **unfractionated heparin** (also known as high molecular weight heparin), **low molecular weight heparin** (LMWH), and **fondaparinux** (ultra-low molecular weight heparin). Unfractionated heparin is referred to as "heparin," or UFH. LMWH heparins are enoxaparin and dalteparin. Fondaparinux is the smallest form of heparin. The pharmacodynamics vary between the heparins, and get rather complicated very quickly. Instead, assume the mechanism of action of all heparins is the same: activation of antithrombin.

What does change between the types of heparin is their convenience. We want you learning that all heparins come down to one of two things: continuous infusion or subcutaneous injection. Unfractionated heparin is administered as a **continuous heparin infusion** ("heparin drip"), given intravenously at a constant rate, and **requires monitoring** during treatment (either active factor 10 levels or PTT can be used). Because it is an infusion, the rate of administration can be adjusted based on the monitoring. Because it is an infusion, **a heparin drip can be stopped**. Heparin infusions are used as **therapeutic heparin only**, and should be seen as a more-difficult-to-use (for the nursing staff, that is) heparin that is chosen when there is a high chance of bleeding. It was the standard heparin to use in the 2000s, but has been replaced by the newer, smaller, more convenient subcutaneous LMWH heparins. **Subcutaneous heparins** boast increased bioavailability and are not given as continuous infusion but as regular injections. These injections can be for either **deep vein thrombosis prophylaxis** or as a **therapeutic heparin**. Enoxaparin, for example, is administered 40 mg once daily as prophylaxis, but as 1 mg/kg BiD for therapeutic intervention. Because it is an injection and not an infusion, once administered, the medication cannot be withdrawn. There is no need to monitor the levels of LMWH.

The **larger the molecule**, the **easier it is to inactivate** with the heparin-reversal agent, **protamine**. Protamine is a positively charged ion that binds to the negatively charged heparin molecule to form a soluble and inactive compound. That means the larger, unfractionated heparin can be more easily stopped (infusion) and more easily reversed (larger), while the smaller heparins are easier to administer, impossible to stop (injection), and more difficult to reverse.

We want you learning that there is a hard separation between factor clots and platelet clots. Heparins are used in the management (and prevention) of deep vein thrombosis and pulmonary embolism. They are administered to stabilize the clot and **bridge to warfarin** (discussed below). You will see unfractionated heparin used in acute arterial disease, especially therapeutic heparin in acute myocardial infarction and peripheral vascular disease. Remember that red clots in the veins and white clots in the arteries are both platelet- and fibrin-based. But, using our organizer, heparins should be considered anticoagulants, blue in color, and treating venous clots.

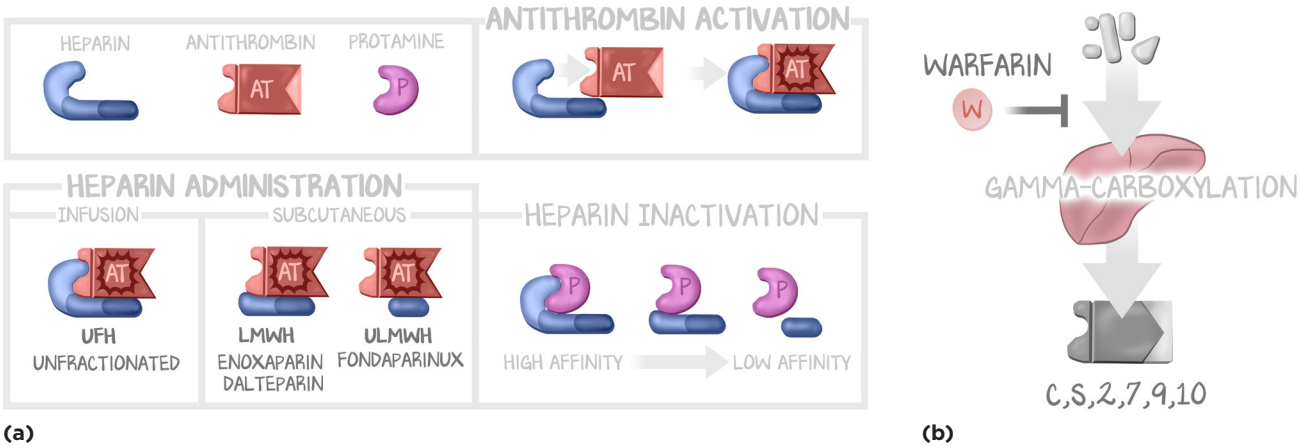

Figure 3.2: Heparins and Warfarin
(a) Heparins, size, and what that means. (b) The mechanism of action of warfarin is to inhibit vitamin K epoxide reductase in the liver.

Anticoagulants #2: Warfarin

Intro. Warfarin is a vitamin K epoxide reductase inhibitor, preventing the γ-carboxylation of the hepatically synthesized factors 2, 7, 9, and 10, and proteins C and S. The decreased synthesis of factors 2, 7, 9, and 10 results in the loss of factors, decreasing the clotting cascade, and results in anticoagulation, the intended effect of warfarin administration. The decreased synthesis of protein C and protein S results in a temporary hypercoagulable state. Warfarin is, and has been, the oral anticoagulant of choice, though in recent years the NOACs have offered fierce competition. Warfarin works. But warfarin is dirty. Its dosing requires titration based on routine monitoring of lab work, has many drug-drug interactions and side effects, and is teratogenic. It is possible to anticoagulate far above the goal, but there are also reversal agents. The pages that follow tease out the many details associated with this paragraph—anticoagulation, procoagulation and the heparin bridge, warfarin reversal, and warfarin side effects.

Anticoagulation. Warfarin is an anticoagulant. It inhibits factors 2, 7, 9, and 10. Even though it does inhibit the synthesis of all four factors, its effects are felt, and measured, by its impact on factor 7, on the extrinsic pathway. We know this because warfarin is monitored using the PT. Only the PT rises in the range of therapeutic warfarin. With warfarin toxicity, both the PT and the PTT rise, the PT more than the PTT; but at therapeutic ranges of warfarin, the PTT does not change. The extrinsic pathway is measured with the PT. Normalizing the PT for international standards gives you the INR. The target anticoagulation is an **INR of 2.0–3.0** for DVT, and higher for higher-risk patients (mechanical heart valves is 2.5–3.5). INR levels must be routinely monitored. Overcoagulation (INR > 5) significantly increases the chances of spontaneous hemorrhage. Warfarin dosing is variable based on diet (leafy greens contain vitamin K, the antidote to warfarin), metabolism of other drugs and alcohol, and varying genetics (warfarin metabolism will remain constant for a given individual, but no two people have the same warfarin metabolism, accounting for wide variation of warfarin dosing). The dose of warfarin is irrelevant. The concentration of warfarin in the plasma is irrelevant. All that matters is the INR, a measurement of how anticoagulated the patient is. The dose is titrated until a steady state is reached, such that the INR is at goal, often resulting in a different dosage taken on different days to achieve the INR. While the PT/INR is used to monitor therapeutic warfarin, as warfarin toxicity worsens and the synthesis of factors 2 and 10 is inhibited, the PTT may rise as well.

Procoagulation. Warfarin causes the inhibition of γ-carboxylation of factors 2, 7, 9, and 10 (leading to the anticoagulant effects) but also the inhibition of γ-carboxylation of **protein C** and **protein S**. Because

protein C and protein S have shorter half-lives than factors 2, 7, 9, and 10, and inhibition of vitamin K epoxide reductase results in reduced factor synthesis, levels of protein C and protein S fall before the clotting factors, leading to a transient **hypercoaguable state** where there is a relative deficiency of the anticoagulant proteins while there still remain some procoagulant factors. In the setting of an active clot, such as in an acute deep vein thrombosis, initiating warfarin without first ensuring adequate anticoagulation with heparin results in expansion of the DVT. The time period between warfarin initialization and being truly anticoagulated is defined by 5 days or a therapeutic INR, whichever is longer. In this hypercoaguable state, adequate anticoagulation is maintained with **therapeutic heparin,** and is thus termed a **heparin bridge**. Heparin bridges the patient from acute thrombosis, through the procoagulant window of warfarin, into the anticoagulation state of warfarin. There are exceptions; e.g., a person on warfarin for primary stroke prophylaxis with atrial fibrillation does not need a heparin bridge. Because of the catastrophic possibilities associated with failing to bridge, we recommend you learn, "all warfarin needs bridging." If you go into a specialty that uses warfarin, learn the exceptions then.

Reversal. Excess anticoagulation can result in hemorrhage and death. Warfarin poisons hepatocytes. Poisoned hepatocytes fail to synthesize clotting factors. When someone is on warfarin and bleeding, the way to fix that is to **give the factors back**. If acutely hemorrhaging and the INR is elevated, give **fresh frozen plasma**, which has factors in it. To restore the function of the hepatocytes, you can use **oral vitamin K**. Vitamin K gives the hepatocytes what they need to make more factors. Vitamin K does reduce the INR, but vitamin K takes a long time to work. It provides hepatocytes with the substrate they need to synthesize proteins. Synthesis of proteins takes time. Therefore, if there is an acute need for factors (the patient is bleeding), use FFP. And, since vitamin K takes a long time to work, there is no reason to give it intravenously. In fact, the only thing you should know about **IV vitamin K is that it causes anaphylaxis**. Oral K only. IV FFP only when bleeding.

Side effects. Warfarin side effects include bleeding, drug-drug interactions, and **skin necrosis**. Skin necrosis happens in people who are **already protein C deficient** (a ridiculously rare inherited disorder). Why cutaneous arteries are affected more than others is unclear. Rarely, patients with protein C deficiency who are placed on warfarin without a heparin bridge can have the same cutaneous process happen in all organs. But, to be clear, the person must already be protein C deficient, be placed on warfarin, be not placed on a heparin bridge, and be unlucky enough to have this happen. In effect, it doesn't happen. What can happen, however, is **teratogenicity**. Warfarin crosses the placenta and can cause hemorrhagic disease in the fetus and prevents γ-carboxylation of proteins in bone, leading to bone malformations. The collection of drug-drug interactions is immense. Warfarin is the prototypical "CYP450-metabolized drug" whose metabolism is altered by other drugs, AND warfarin is the prototypical "displaced-from-albumin drug" whose distribution is altered by other drugs. Warfarin is metabolized by the CYP450 enzyme **2C9** (the only P450 enzyme we recommend memorizing). The P450 **inducers** would clear warfarin faster, so would decrease the PT. They are **barbiturates**, **cholestyramine**, and **rifampin**. The P450 inhibitors would cause metabolism to be reduced, increasing the PT. P450 inducers that affect warfarin are **alcohol**, **metronidazole**, **TMP/SMX**, **amiodarone**, and **cimetidine** (the only H_2 blocker that induces P450 and the only H_2 blocker never prescribed, but commonly appears on tests).

Anticoagulants #3: Other Orals Not Warfarin

The NOACs (formerly Novel Oral AntiCoagulants, now Non-vitamin-K-epoxide-reductase-inhibitor Oral AntiCoagulants) come in two forms—**direct 10a inhibitors** that target activated factor 10, and **direct thrombin inhibitors** that target activated factor 2, also called thrombin. For the basic sciences, you are expected to learn them as two different classes of medications. However, we teach them to you as NOACs because that's how you will use them clinically. NOACs are interchangeable with each other and are effectively the option other than warfarin for anticoagulation.

They do **not need to be bridged** like warfarin needs to be bridged, **require no monitoring** like warfarin requires monitoring, and are **unaffected by diet** unlike warfarin is affected by diet. There are fewer side effects and drug-drug interactions. However, until recently there was **no reversal**. Even now, reversal agents are expensive and far less effective than FFP is at reversing warfarin.

The direct 10a inhibitors, rivaro**Xa**ban and api**Xa**ban (they have Xa, for 10a, in their name) can be reversed with andexanet alfa. The direct thrombin inhibitor dabigatran can be reversed with the monoclonal antibody idarucizumab.

Anticoagulants #4: Direct Thrombin Inhibitors That Aren't Oral

Until 2012, there were two intravenous direct thrombin inhibitors: lepirudin and argatroban. Lepirudin was removed from the market in 2012. Its cousin bivalirudin is used in cardiac stents and will never be the right answer on your tests.

Therefore, the only parenteral direct-thrombin inhibitor is **argatroban.** It has exactly one use. If a patient is on heparin and develops heparin-induced thrombocytopenia (as evidenced by a drop in platelets and a new venous thrombus), they require intravenous anticoagulation for the acute thrombosis, but cannot receive heparin. The NOACs, being oral, do not act quickly enough, nor do they reach effective steady-state concentrations soon enough.

HEPARINS	WARFARIN	10A-INHIBITORS	THROMBIN INHIBITORS
Unfractionated (IV)	Warfarin	RivaroXaban (PO)	Dabigatran (PO)
Dalteparin (SubQ)		ApiXaban (PO)	Argatroban (IV)
Enoxaparin (SubQ)			
Fondaparinux (SubQ)			

Table 3.1: Anticoagulants

Antiplatelet #1: Aspirin (and NSAID Side Effect)

Aspirin, abbreviated ASA, **irreversibly inhibits COX-1** and **COX-2**, the first steps of the arachidonic acid pathway. In doing so, it has a number of downstream effects. One outcome of the arachidonic acid pathway is thromboxane A_2. In platelets, TXA_2 is within α-granules and is involved in platelet activation. Aspirin's intended effect is the decreased synthesis of TXA_2, and therefore, in effect, reduced TXA_2-receptor stimulation, and therefore **reduced platelet activation**. Aspirin is the prototypical antiplatelet, used in every instance of atherosclerotic vascular disease. It is the first-line agent in coronary artery disease, cerebrovascular disease, and peripheral vascular disease.

Because aspirin effect is at the top of the arachidonic acid pathway, it is nonselective. The impaired arachidonic acid pathway in other tissues unrelated to TXA_2 is what causes the other effects of aspirin. The inhibition of **prostacyclins** reduces inflammation and limits fever, allowing aspirin to be used as a fever reducer. The inhibition of **prostaglandins** reduces inflammation and pain and allows aspirin to be used as a pain reliever. However, the same inhibition of prostaglandins in the stomach causes **gastric ulcers** and gastritis. Aspirin is extremely toxic. Overdose results in a respiratory alkalosis at low doses through a mechanism you need not familiarize yourself with. As the concentration of aspirin, also known as salicylate or salicylic acid, rises to fatal levels, the patient will present with an **anion gap metabolic acidosis**.

NSAIDs, non-steroidal anti-inflammatory drugs, also **inhibit COX-1** and **COX-2**, but do so **reversibly**. NSAIDs are **not antiplatelets**. One of the potential side effects of NSAIDs is bleeding, and that bleeding will be of the platelet type, but NSAIDs are **pain relievers** and **fever reducers**, given their effect on prostaglandins. They have **anti-inflammatory** effects, given their inhibition of prostacyclins. They are not ever used, however, as an antiplatelet. In fact, the COX-2 selective inhibitor **celecoxib** has CAUSED myocardial infarctions. Celecoxib was invented to escape gastric ulcer side effects (from inhibited prostaglandins).

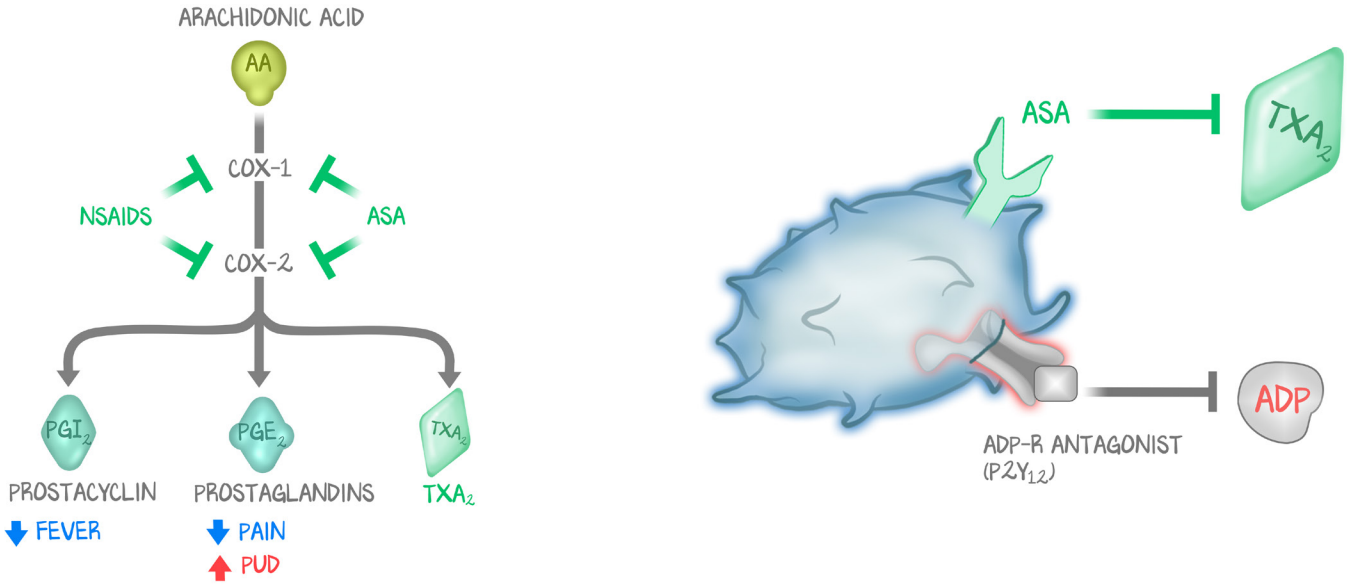

Figure 3.3: Arachidonic Acid Pathways and Platelet Activation
(a) Arachidonic acid pathway without the complexities. (b) Activation of platelets from TXA_2 blocked by aspirin and ADP blocked by ADP-R-antagonists.

Antiplatelet #2: ADP-$P2Y_{12}$ Receptor Antagonists

Platelets are the main cause of arterial platelet clots; aspirin successfully manages platelet clot diseases; but aspirin presents a variety of unintentional consequences. Therefore, additional medications were synthesized to inhibit platelet activation. We taught you two receptors that activate platelets—TXA_2 (blocked by aspirin) and ADP. Specifically, the $P2Y_{12}$ receptor is activated by ADP, which subsequently leads to the activation of glycoprotein 2b/3a. You may see "ADP receptor" or you may see "$P2Y_{12}$." So, we always combine them to ensure that you learn them as the same thing: ADP-$P2Y_{12}$. Aspirin does indeed block TXA_2, but by blocking an upstream pathway in its synthesis, thus the additional side effects. ADP-$P2Y_{12}$ receptor antagonists target the platelets directly, **irreversibly inhibiting** the receptor, providing the antiplatelet mechanism of aspirin but escaping the side effects, and therefore are tolerated much better than aspirin. Binding to the ADP-Receptor results in expression of glycoprotein 2b/3a on the plasma membrane surface. Blocking that prevents that expression, and prevents aggregation.

In **coronary artery disease**, in those who receive a stent, bypass, or medical management, **dual antiplatelet therapy** is absolutely indicated for life. The only reason to discontinue dual antiplatelet therapy is bleeding. The only side effect of ADP-$P2Y_{12}$-R inhibition is bleeding. If a drug-eluting stent is placed (the angioplasty intervention with the lowest relapse rate), dual antiplatelet therapy **is required for a year** to prevent in-stent stenosis. In CAD of any kind, dual antiplatelet therapy is **recommended for life**.

In **peripheral vascular disease**, dual antiplatelet therapy is also indicated for life. In **stroke** there is currently a debate whether dual antiplatelet therapy is beneficial or simply increases bleeding risk without preventing the next stroke. The current practice is to do dual antiplatelet therapy if a stroke occurs on aspirin. Which means, the data we have that says, "dual antiplatelet therapy may not work," includes patients who had a stroke once, got put on aspirin, had another stroke, and had ADP-R-i added, then had yet another stroke on both. When other vascular disease shows improvement, but stroke may not, we stick with, "all vascular disease should get dual antiplatelet therapy," and find reasons not to do both in individual patients. But in your career, that may change.

Examples include **clopidogrel**, **prasugrel**, and **ticagrelor**.

Antiplatelet #3: Glyc2b/3a Inhibitors

These drugs exist. They are used only in highly specialized situations, such as during coronary angioplasty. You are likely never to see them used in clinical practice. But with such a clear mechanism, and a disease state that accompanies glycoprotein 2b/3a (Glanzmann's thrombasthenia), it is easy to test you on the drug's mechanism. Be able to identify **abciximab** (abc-ixi-monoclonal-antibody), pronounced "ab-six-i-mab," and **tirofiban**. Abciximab is the drug used in cath labs; tirofiban looks like it would be one of those NOACs, and is a sound-alike, look-alike distractor.

Fibrinolytics #1: tPA

Tissue plasminogen analogs are discussed in stroke treatment. Streptokinase, alteplase, or simply tPA are intravenous preparations that activate plasmin. They can be used intra-arterially for localized dissolution of acute thrombosis, but are administered intravenously for stroke, myocardial infarction when percutaneous coronary intervention isn't possible, and for massive pulmonary embolism. There is a high risk of bleeding and an extensive checklist before giving them.

Fibrinolytics #2: Antifibrinolytics

Gave too much tPA? Gave tPA and the patient started bleeding? Are they on one of those agents that cannot readily be turned off? Plasminogen was turned to plasmin. Plasmin is degrading any clot that forms. One thing you could do is inhibit plasmin, thereby preventing the degradation of any existing or new clots. We don't have any direct plasmin antagonists, but we do have drugs that **inhibit the conversion** of plasminogen to plasmin. Whatever plasmin there already is will degrade whatever clots are already there. But without any new plasmin (plasmin activation blocked by the drug), any new thrombus formed after would not be degraded. Attempting this is only safe to do in a situation where the patient is already suffering from hemorrhage, as giving this medication to someone not already bleeding from too much plasmin will cause that person to become hypercoagulable and clot everywhere. Drugs that reverse tPA are **aminocaproic acid** and the oral form **tranexamic acid**. Support with cryoprecipitate and FFP is started first, though these agents are associated with tPA administration overdose, making them clearly the right answer in a test question mentioning what to do after receiving excess fibrinolytics.